# Long-term hepatotoxicity of azathioprine, 6-mercaptopurine and 6-thioguanine in IBD patients

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Assess hepatotoxicity of long-term azathioprine and 6-mercaptopurine use in IBD-patients as compared with a cohort of long-term 6TG users

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Gastrointestinal inflammatory conditions |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON55534

**Source**
ToetsingOnline

**Brief title**
LONGTOX

### Condition

- Gastrointestinal inflammatory conditions
- Hepatic and hepatobiliary disorders

**Synonym**
hepatotoxicity, liver injury

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Vrije Universiteit Medisch Centrum
**Source(s) of monetary or material Support:** HLW bv;Helmond;The Netherlands,HLW pharma bv

## Intervention

**Keyword:** Hepatotoxicity, Inflammatory bowel diseases, Thiopurines

## Outcome measures

### Primary outcome

The primary endpoint is histological assessed NRH

### Secondary outcome

- liver stiffness assesed by Fibroscan (if available)

- endosonographically determined liver and spleen size and liver appearance

- Standard laboratory tests, including liver tests and full blood count.

# Study description

### Background summary

Hepatotoxicity during thiopurine therapy, of which the pathogenesis has not completely been elucidated, is a well-known adverse event that frequently results in thiopurine withdrawal. Nodular regenerative hyperplasia (NRH) of the liver is a histopathological condition that has been associated with the use of thiopurines and in particular with 6-thioguanine (6-TG). 6-TG has been proposed to function as a rescue drug in case of intolerance to the other immunomodulators. However, the occurrence of NRH led to rejection of 6-TG. Not only with 6-TG but also with classical thiopurine therapy has NRH been described, albeit less frequent. It is likely that during AZA and 6-MP therapy NRH is more frequent present as NRH initially does not go together with clinical symptoms. However, studies as performed with 6-TG on the incidence and prevalence of NRH during AZA and 6-MP are scarce. As thiopurines are being prescribed for longer periods, there is a compelling need for long term safety data. Furthermore, more adequate dosed 6-TG may not be so strongly related with histological abnormalities of the liver as compared with the classical thiopurines.

### Study objective

Assess hepatotoxicity of long-term azathioprine and 6-mercaptopurine use in IBD-patients as compared with a cohort of long-term 6TG users

### Study design

This study will be a multi-center observational cross-sectional case-control study. Each study subject will visit the hospital once within the scope of this study. This study ends when the number of included participants reaches the calculated number.

### Study burden and risks

The patients will be asked to visit the hospital for one day. They will undergo a Fibroscan (not in every participating hospital) and an ultrasonography of the spleen and liver and subsequently a liver biopsy will be performed. (1.0% major complication) Blood will be drawn by one venous puncture, physical examination will be performed and a questionnaire will be conducted.
The benefit of participation is that liverbiopsies could reveal histological abnormalities which require dose adjustments of the thiopurine therapy and thereby reduce the worsening of the liver abnormalities. Also knowlegde on this topic is of major importance for future thiopurine prescriptions in IBD patients.

## Contacts

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## Trial sites

### Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Crohns disease or ulcerative colitis; age between 18 and 70 years; AZA , 6-MP or 6-TG therapy for more than five years succesively; written informed consent

## Exclusion criteria

anaemia (Hb<6.5mmol/l), thrombopenia (<50x10*9/l), contra-indications to undergo a liver biopsy

# Study design

## Design

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| Study phase: | 4 |
| Study type: | Observational invasive |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 29-09-2009 |
| Enrollment: | 114 |
| Type: | Actual |

## Ethics review

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| Approved WMO Date: | 07-09-2009 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 24-04-2010 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 27-04-2010 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 09-06-2011 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 08-03-2017 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 17-10-2017 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 14-03-2019 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 14-02-2020 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 11-03-2021 |

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| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 23-12-2021 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| CCMO | NL23867.029.08 |